

Inflammatory bowel disease and irritable bowel syndrome: separate or unified?

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Both irritable bowel syndrome and inflammatory bowel diseases share symptoms of altered bowel habits associated with abdominal pain or discomfort. Irritable bowel syndrome has been referred to as a functional bowel disorder, which is diagnosed by a characteristic cluster of symptoms in the absence of detectable structural abnormalities. Inflammatory bowel disease is a heterogeneous group of disorders characterized by various forms of chronic mucosal and/or transmural inflammation of the intestine. In this review, the authors discuss recent evidence suggesting several potential mechanisms that might play a pathophysiologic role in both syndromes. Possible shared pathophysiologic mechanisms include altered mucosal permeability, an altered interaction of luminal flora with the mucosal immune system, persistent mucosal immune activation, alterations in gut motility, and a role of severe, sustained life stressors in symptom modulation. It is proposed that similarities and differences between the two syndromes can best be addressed within the framework of interactions between the central nervous system and the gut immune system. Based on recent reports of low-grade mucosal inflammation in subpopulations of patients meeting current diagnostic criteria for irritable bowel syndrome, therapeutic approaches shown to be effective in inflammatory bowel disease, such as probiotics, antibiotics, and antiinflammatory agents, have been suggested as possible therapies for certain patients with irritable bowel syndrome.

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Abbreviations

HPA	hypothalamic-pituitary-adrenal
IBD	inflammatory bowel diseases
IBS	irritable bowel syndrome
IELs	intraepithelial lymphocytes
INOS	inducible nitric oxide synthase
MAPK	mitogen-activated protein kinase
PI-IBS	postinfectious irritable bowel syndrome
Th1	T helper 1
TNF- α	tumor necrosis factor- α

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Inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS) represent two conditions characterized by chronically recurring symptoms of abdominal pain, discomfort (urgency and bloating) and alterations in bowel habits. However, whereas IBD is characterized by inflammation or ulcerations in the small and/or large intestine, such “organic” changes have traditionally not been associated with IBS. IBD is usually classified as ulcerative colitis or Crohn disease, but it also includes forms of microscopic colitis, *eg*, histologic evidence of mucosal inflammation without macroscopic abnormalities. IBD is characterized by a constellation of patient-reported history and endoscopic, histopathologic, and radiologic findings, often with serologic correlates. Classic signs that reflect the inflammatory process within the gastrointestinal tract are rectal bleeding, diarrhea, fever, and weight loss, occasionally associated with extraintestinal manifestations. Interestingly, in the absence of complications, abdominal pain is not necessarily the most prominent symptom in IBD, despite extensive mucosal inflammation and presumably sensitization of peripheral visceral pain pathways. Genetic predisposition, environmental factors, infectious agents, altered gut epithelial permeability, and impaired immune responses have been incriminated in the still unclear cause of IBD.

By contrast, IBS, classified as functional (as opposed to organic) bowel disorder, is currently diagnosed on the basis of a characteristic cluster of symptoms in the absence of detectable structural abnormalities. As a matter of fact, according to the currently used symptom criteria (Rome criteria), once organic changes are detected, a diagnosis of a functional syndrome can no longer be made [1]. Because of the nonspecificity of the cardinal symptoms of abdominal pain or abdominal discomfort (the latter including bloating-type symptoms, a sensation of rectal urgency, or incomplete evacuation), the current diagnosis of IBS applies to a heterogeneous group of patients, even after attempts to define subgroups based on predominant bowel habit. Current theories to explain the pathophysiology of IBS include alteration in visceral perception, gastrointestinal motility and gut epithelial and immune function. Considerable evidence supports a role of psychosocial and physical (*ie*, gastroenteric infections) stressors as central and peripheral triggers, respectively, of first symptom onset or exacerbation [2•]. As reflected by an increasing number of publications on the subject, considerable interest in the putative role of low-

grade chronic inflammation in the pathogenesis of IBS has recently emerged [3]. Enhanced responsiveness to psychosocial and physical stressors has been suggested as a plausible mechanism that could explain most clinical and experimental findings in IBS, and that is consistent with the majority of the reported physiologic alterations [4].

Evidence of mucosal immune activation in patients meeting symptom criteria for inflammatory bowel diseases

Several recent independent studies have demonstrated alterations in the gut-associated immune system. Quantitative assessment in unselected patients with IBS have shown increased mast cell numbers in the ileum [5] and colonic mucosa [6]. Preliminary evidence suggests an increase of overall cellularity in the colonic mucosa [7] and a higher number of mast cells containing tryptase (known to have proinflammatory effects) in the colonic lamina propria of patients with IBS [8]. Additional preliminary results indicate a significant increase of inducible nitric oxide synthase (iNOS) expression in the colonic mucosa from unselected patients with IBS compared with control patients [9]. In the human colon, upregulation of iNOS has been implicated in inflammatory processes, and increased expression has been documented in IBD [10]. More recently, a study by Chadwick *et al.* [11•] demonstrated intestinal mucosal immune activation in 77 symptomatic patients meeting the Rome criteria (the authors did not specify Rome I vs II criteria). The study included patients with diarrhea, constipation, or both. In 38 of the patients (50%), a normal conventional histologic appearance was seen, but the immunohistologic results were abnormal (intraepithelial lymphocytes-IEL, lamina propria CD25+ and CD3+ lymphocytes). In 40% of patients, nonspecific microscopic inflammation was seen, whereas immunohistologic results showed similar increases in lymphocyte populations as in the first group. However, in contrast to the first group, they also showed increased numbers of neutrophils and mast cells. Ten percent of patients fulfilled the histologic and immunohistologic criteria for lymphocytic colitis. Even though the magnitude of changes in cell numbers was far less than observed in patients with IBD, the increased numbers of IEL, T cells, IL-2 receptor expressing cells, suppressor/cytotoxic T cells, and NK cells were consistent with an increased inflammatory cell presence in a subset of patients with altered bowel habits who met the symptom-based Rome criteria. Because a significant number of patients meeting the Rome criteria also met the histologic criteria for a diagnosis of lymphocytic colitis, the findings highlight a major problem with the way we currently diagnose IBS. By definition, the diagnosis of an organic disease such as lymphocytic colitis is inconsistent with a diagnosis of IBS. Furthermore, it is unclear whether the patients met the Rome criteria because of the presence of discomfort (urgency, bloating) relieved by bowel movements, or whether they re-

ported abdominal pain. Using the current Rome criteria, a diagnosis of IBS can be made in any patient experiencing abdominal discomfort (for example, in the form of urgency or bloating-type symptoms), that is relieved by a bowel movement. In the absence of mucosal histology to rule out macroscopic or microscopic forms of colitis, such a symptom cluster is likely to include a wide range of syndromes with different causes and pathologic mechanisms.

Another study reported neuromuscular and inflammatory abnormalities in the small bowel of 10 patients (8 women; age range 24–55 years) with severe IBS symptoms [12]. Surprising for an IBS population, the symptoms apparently were severe and refractory enough to justify a laparoscopic full-thickness biopsy. The durations of IBS symptoms ranged from 2 to 30 years, and the predominant bowel habits included constipation, diarrhea, and alternating bowel habits. In this study, analysis of full-thickness biopsy specimens of the jejunum from IBS patients (diagnosis having been made on the basis of absence of detectable structural lesions and fulfillment of the Rome I criteria for IBS) showed several histopathologic abnormalities. The authors reported in most patients some neural degeneration in the ganglia of the myenteric plexus associated with infiltration of CD3+ T lymphocytes and longitudinal muscle hypertrophy. In some cases, IEL numbers were increased, and the numbers of interstitial cells of Cajal were also increased. There are two major problems with the reported findings. First is the absence of an appropriate control group. For example, the observed mucosal alterations in the *proximal jejunum* were compared with biopsy specimens obtained from the *distal ileum* during colonoscopy, and alterations in the jejunal wall were compared with findings obtained in tissues from deceased patients (of unspecified sex and age). Second, as admitted by the authors, the patients in this study represented a highly selected group with severe symptoms that were apparently refractory to current management. Even though it was stated that patients had normal or nonspecific changes on small intestinal manometry, it is conceivable that the patients had a mild or early form of chronic intestinal pseudoobstruction. Analogous to the comments made above about the nonspecificity of the Rome criteria to differentiate microscopic colitis from IBS, the same argument could be made for chronic intestinal pseudoobstruction.

Patients in another group, frequently discussed as evidence for a possible role of altered gut immune function in IBS, are those in whom IBS-like symptoms develop after a documented gastroenteric infection (so-called postinfectious IBS [PI-IBS] patients). A history of acute gastroenteritis caused by a variety of bacterial infections as well as parasitic infections was found to increase the risk of the development of persistent IBS symptoms.

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The risk factors associated with PI-IBS include female gender, duration of the acute illness episode, and a major stressful life event at the time of the infection. Patients with PI-IBS have been reported to show changes in gut motility (eg, reduced rectal compliance) and epithelial function and an increase in enterochromaffin cells [13,14]. In addition, mucosal immune parameters in these patients exhibit changes that include altered macrophage (CD68) and T lymphocyte (CD3, CD4, CD8) populations and increased expression of IL-1 β mRNA [15]. Some of these changes, as well as symptoms of diarrhea, were shown to persist for more than a year in some cases, suggesting chronic immune system activation [15]. Although the mechanisms involved in the ongoing inflammation after clearance of the infectious agent remain unclear, it has been suggested that a subset of IBS patients may have a genetic predisposition to inflammatory dysregulation. Preliminary evidence suggests a reduced frequency of the high producer allele for the antiinflammatory cytokines IL-10 and TGF- β , suggesting a reduced production of these cytokines in patients with IBS compared with healthy control subjects [16]. Several important questions have to be addressed before the existence of a distinct pathophysiologic entity of PI-IBS can be confirmed. (1) Even though persistence of low-grade inflammation has been described in individuals who continued to be symptomatic, a causal role of these mucosal changes with IBS symptoms has not been demonstrated [14,15]. Preliminary reports from a therapeutic trial with an antiinflammatory agent in PI-IBS did not demonstrate any effect on symptoms [17]. (2) There is currently no evidence of visceral hypersensitivity in this patient group, and the reported lower volume thresholds for discomfort simply reflect a reduced rectal compliance. (3) It is unclear whether patients who report their first onset of IBS symptoms after an enteric infection have a history of other intestinal or extraintestinal functional syndromes (such as dyspepsia or chronic constipation) or anxiety disorders. In this case, the persistence of bowel symptoms may simply be a reactivation of a preexisting functional syndrome.

Tibble *et al.* [18••] compared a large population of patients with altered bowel habits meeting the Rome I criteria for IBS and patients with different organic diseases of the intestine, including IBD, cancer, infectious diarrhea, and celiac disease. They observed that markers for intestinal inflammation, such as fecal calprotectin levels, were elevated in the majority of patients with organic gastrointestinal conditions and decreased in the majority of patients with IBS. The sensitivity and specificity of fecal calprotectin levels for organic intestinal disease were 89% and 79%, respectively. However, the authors observed a significant number of IBS patients whose fecal calprotectin levels were above a normal cutoff value, suggesting some degree of inflammation.

Taken together, the above findings are most consistent with the concept that in a subset of patients meeting the current diagnostic criteria for IBS, chronic low-grade immune activation may be associated with chronic changes in gut motor and secretory function resulting in chronic abdominal discomfort associated with altered bowel habits. However, a causal relationship between visceral hypersensitivity and chronic immune activation has not been demonstrated.

Altered immune system and inflammation in inflammatory bowel diseases

Classic histopathologic inspection of tissue from patients with IBD reveals vasodilatation, venocongestion, edema, infiltration of large numbers of inflammatory cells (lymphocytes as well as macrophages and monocytes), and architectural disarray, often with mucosal erosions and/or frank ulcerations. Although the causative triggers remain unclear, the role of a persistent and likely dysregulated mucosal immune response is central to the pathogenesis of IBD. However, it remains unclear whether the persistent inflammation, an intrinsic feature of IBD, reflects a primary aberration in mucosal response or results from an inappropriate persistent stimulation. Accumulating evidence indicates that excessive activation of immunoinflammatory responses in IBD may be initiated by luminal flora. In this regard, recent data showed no difference in the overall composition of mucosal flora in patients with IBD and control subjects but demonstrated a higher concentration of mucosa-associated bacteria in patients with IBD [19]. The authors suggest that the changes in the concentrations of mucosal flora in IBD are not secondary to inflammation but result from a host-specific altered immunoinflammatory mucosal response to "self-flora" in susceptible individuals. The role of genetic factors continues to be explored, with disease susceptibility associated with genetic markers for particular subsets of IBD patients. Recent studies using genome-wide screening provided the first link between NOD2 mutations and the clinical characterization of Crohn disease [20,21]. NOD proteins are thought to be cytosolic receptors for bacterial signals, and NOD2 is expressed in monocytes and activates nuclear factor κ B (NF- κ B). However, the mechanisms by which NOD2 mutations contribute to Crohn disease need further investigation. It has been hypothesized that different concentrations of bacteria in the ileum relative to the colon may contribute to the association between NOD2 mutations and ileal disease. A genetic background was also identified in ulcerative colitis associated with HLA genes and regions of the chromosomes 3, 7, and 12 [22]. In a recent review, Ardizzone *et al.* [23••] compiled the genetic factors recently involved in the pathogenesis of IBD. Considering the central role of cytokines in modulating intestinal inflammation, several studies have focused on cytokine genes, looking for mutations or polymorphisms and expression dysregulation [24]. In Crohn disease, an in-

creased expression of T-helper-1 (Th1) cytokines was initially described, whereas an atypical Th2 response was associated with ulcerative colitis, but this assessment is now thought to be too simplistic. Cytokine gene-regulated differences between and within the diseases are clearly more complex. Advances in the understanding of the immune response in IBD have stimulated the development of new therapeutic agents directed against key players in the inflammatory process. A range of therapeutic strategies to block the biosynthesis or action of proinflammatory cytokines, acting directly or through targeting immunoregulatory cytokines, has been developed [25].

Among specific targets, tumor necrosis factor- α (TNF- α) was among the first mucosal cytokines identified as critical in the development and amplification of mucosal inflammation in IBD [26]. Recent clinical trials showed that anti-TNF- α antibodies provide marked clinical benefits in some patients with Crohn disease: a translational insight that has now become commonplace in IBD clinical therapy [27,28]. An inhibitor of mitogen-activated protein kinase (MAPK) appears to be another candidate in novel therapeutic strategies. A beneficial effect of CNI-1493 (MAPK inhibitor) in patients with severe Crohn disease was recently described [29]. A better characterization of the molecular signaling pathways involved in the activation of key immune and inflammatory cells will undoubtedly provide new targets for the development of therapeutic agents for IBD.

What unifies and separates irritable bowel syndrome and inflammatory bowel diseases

Possible role of failure to downregulate immune response

A comparison of published data on the activation of the gut-associated mucosal immune system in IBS and IBD reflects both the similarities and the differences in the altered immune response observed in these disorders. However, the triggering factor initiating the inflammatory response remains unclear. In IBS, an immune response to infection [30], a disinhibition of the immune system during chronic sustained stress (Fig. 1), or a combination of both are plausible mechanisms that could result in the initial immune activation. The persistence of low-grade inflammation after pathogen clearance or after resolution of the psychosocial stressor, in a subset of individuals, may be related to an inability to efficiently downregulate the inflammatory response. This inability may be related to genetic factors or to early programming of antiinflammatory systems, such as the hypothalamic-pituitary-adrenal (HPA) [31•]. For example, a hyporesponsive HPA axis in the Lewis rat has been shown to be associated with exaggerated immune responses to various stimuli, including chemically induced colitis [32]. The most recent available data on IBD increasingly em-

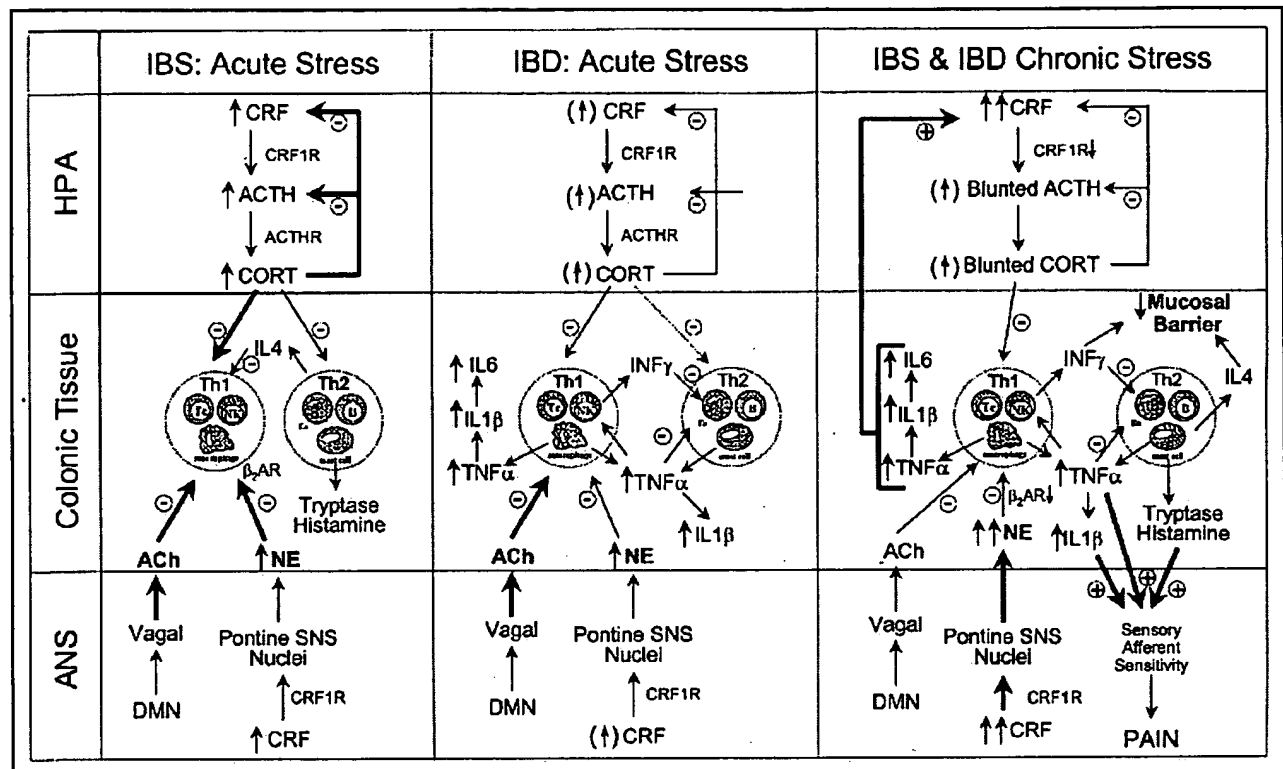
phasize the role of immunogenetics in the predisposition, modulation, and perpetuation of the disease [33]. The abnormal amplification and persistence of inflammation leading to tissue injuries likely reflects the continuing presence of the driving stimulus and self-reinforcing activation of mucosal inflammatory cells mediated by increased expression of cytokines.

Increased permeability

For both syndromes, histologic and functional alterations of the mucosal barrier have been recently reported [11•,12,24,25]. Small intestinal permeability is abnormal in a wide variety of conditions affecting the small intestine, including celiac disease, Crohn disease, and intestinal infections [18••]. Interestingly, gut permeability assessed by the lactulose/mannitol ratio is significantly elevated in PI-IBS patients [15]. This functional alteration of the intestinal barrier function may be a cause or consequence of inflammation, and a direct link between increased intestinal permeability and the exaggerated immune activation in IBD still needs to be confirmed. In addition to a causative role of peripheral factors, gut permeability changes in animal models have also been reported in response to various stressors. For example, in a rat model of chronic stress, an increase in intestinal epithelial permeability, associated with an increase in mucosal neutrophils and mast cells, has been demonstrated [34••]. In this model, the combination of stress-induced increases in intestinal permeability, allowing easier access of antigens to gut-associated macrophages and dendritic cells, together with stress-induced changes in HPA axis responsiveness and cytokine profiles, resulted in the development of colitis, without any additional chemical or immunologic manipulations. Rats with a history of aversive early life events were more susceptible to these stress-induced changes in gut permeability [35•], possibly related to early programming of the HPA axis [31•].

Changes in luminal flora

A change in intestinal microflora has been implicated, in association with genetic factors, as a putative mechanism responsible for the initiation and persistence of inflammation in IBD. Indeed, it has been suggested that the failure to maintain immunologic tolerance toward the indigenous microflora leads to a disease-associated dysregulation of the gut-associated immune system. Direct and indirect evidence of altered flora of the large and small intestine has been reported in IBS patients. For example, Balsari *et al.* [36] observed a decrease in coliforms, lactobacilli, and, to some extent, bifidobacteria in a small group of IBS patients. More recently, preliminary evidence of an alteration of bacterial concentration in colonic biopsy specimens from IBS patients has been reported [37]. Indirect evidence for bacterial overgrowth of the small intestine (in the form of altered hydrogen breath test results) has been reported in patients with IBS, and a recent randomized controlled trial found evi-

Figure 1. Brain-gut immune interactions in irritable bowel syndrome and inflammatory bowel disease: effect of chronic stress on the mucosal immune system

Acute stress causes increases in the activity of the hypothalamic-pituitary-adrenal (HPA) axis and of the two branches of the autonomic nervous system (ANS), the sympathetic nervous system (SNS), and the parasympathetic (vagal) system. In patients with irritable bowel syndrome, the peripherally acting products of each of these pathways (cortisol, CORT; norepinephrine, NE; acetylcholine, ACh) can inhibit the mucosal immune system, especially Th1-type responses. This results in a temporary shift toward Th2 cytokine responses (IL-4 and others) that are not as strongly inhibited and that can further inhibit Th1 responses. In patients with inflammatory bowel diseases, the corticotropin-releasing factor (CRF) response may be blunted, leading to diminished CORT and NE release. These changes favor the production of Th1 cytokines and the proliferation of macrophages, natural killer (NK) cells, and cytotoxic T cells (Tc). TNF α , which is produced by activated macrophages but can also be released by activated mast cells, stimulates the production of IL-1 β (in the Th1 pathway) and IL-6 (by lymphoid and nonlymphoid tissues). With chronic stress in both types of patients, the shift to a Th1 response becomes predominant, with positive feedback loops developing between the gut and the brain. The restraints on immune cell proliferation and activation are compromised by blunting of the HPA axis response due to downregulation of pituitary CRF1 receptors, decreased vagal tone, and downregulation of β 2-adrenergic receptors (β 2-AR) on Th1 immune cells by chronically elevated catecholamines. Circulating levels of TNF- α , IL-1 β , and IL-6 increase to concentrations that synergistically stimulate CRF production in the PVN of the hypothalamus. In irritable bowel syndrome, TNF α and IL-1 β sensitize primary afferent terminals through long-lasting effects on gene expression, including the expression of neurokinin receptors. Locally acting mast cell products (tryptase and histamine) and proinflammatory compounds (PGE $_2$) can also sensitize primary afferents. Both IFN γ (Th1 cytokine), which is produced by NK cells in response to TNF α , and IL-4 (a Th2 cytokine) have been shown to decrease mucosal barrier function by increasing epithelial permeability [54,55], thus perpetuating a local inflammatory response by allowing entry of bacteria and bacterial products. Subjective pain responses to peripheral sensitization of visceral afferents in irritable bowel syndrome and inflammatory bowel diseases are likely to be modulated differentially by endogenous pain modulation pathways. DMN, dorsal motor nucleus of the vagus; ACTH, adrenocorticotropin hormone.

dence that antibiotic treatment was beneficial for IBS symptoms of bloating and discomfort [38]. Based on the concept of altered interactions between the colonic flora and the gut-associated immune system, probiotics have been proposed as an alternative strategy for the treatment of several gastrointestinal diseases, including IBD [39] and more recently IBS [40,41]. However, the reported results are conflicting, and only a small number of double-blind controlled clinical trials support a beneficial health effect in IBD or IBS [42]. The epithelium has recently been recognized as playing an important role in innate immune responses in response to intestinal microorganisms [43,44]. It expresses a variety of receptors (Toll-like receptor) involved in the recognition of a spectrum of microbial products. This recognition capability

may enable an appropriate cytokine and chemokine secretion in response to changes in luminal flora.

Influence of sustained psychosocial stressors on mucosal immune system activation

Even though stress has been less recognized as a factor in the natural history of IBD, considerable evidence supports a prominent role for it in the pathophysiology and clinical presentation of both IBD and IBS symptoms [45]. Patients with IBS seem to have a greater reactivity to stress than do control subjects or IBD patients. Yet, sustained psychologic stressors have been associated with the onset and exacerbation of symptoms in both IBS and IBD [46–48]. The development of persistent IBS symptoms after acute gastroenteritis has been asso-

ciated with major life events around the time of infection [14]. Similarly, for IBD, a wide range of clinical studies indicates a strong link between sustained psychosocial stressors and IBD activity [49]. Levels of long-term perceived stress have been shown to correlate with changes in mucosal appearance and relapse in ulcerative colitis [50]. Further evidence of an influence of stress on inflammatory processes comes from animal studies showing a modulation of the immune function at different levels, including immune cell distribution, cytokine profiles, or susceptibility to infection in naïve or colitic animals [51]. In view of the established concept of an altered immune response in IBD patients, and the suspected low-grade inflammation in some patients meeting the symptom criteria for IBS, it is reasonable to consider a bidirectional model of brain-gut interactions as an important determinant of gut-associated immune activation in both disorders.

Chronic inflammation and alteration of sensory-motor functions of the gastrointestinal tract

Despite the common assumption that chronic gut mucosal inflammation is associated with sensory-motor dysfunction of the gastrointestinal tract in inflammatory as well as functional intestinal disorders, the relationship between *chronic* inflammation and the generation of gastrointestinal symptoms remains unclear. The development of IBS-like symptoms in some patients with quiescent ulcerative colitis was suggested as an indication of the role of inflammation on altered sensory and motor function [8]. The concept of long-lasting postinflammatory changes in gut motility is supported by the observation of altered anorectal and colonic motility in patients in remission from ulcerative colitis and Crohn disease [52]. However, chronic abdominal pain and visceral hypersensitivity—classic features in patients with IBS—do not appear to be a hallmark of ulcerative colitis or Crohn disease [53]. One may speculate that various patient populations with different degrees of intestinal inflammation (patients with IBD and PI-IBS, and possibly small subsets of those with IBS) do not necessarily experience pain and discomfort from these mucosal changes. Whereas the effects of the immune activation are likely to affect enteric nervous system circuits and smooth muscle function, altering intestinal compliance and reflex activity and producing such symptoms as diarrhea and urgency, the effects on visceral perception are less predictable. An important variable in symptom generation is the differences in the ability of the brain and its endogenous pain inhibitory pathways to counteract the changes in peripheral viscerosensory pathways.

Conclusion

The recent observation of an activated immune system in some IBS patients associated with persistent low-grade mucosal inflammation provides evidence for the reconsideration of the symptom-criteria-based diagnosis

of functional bowel disorders. The development and use of biologic markers identifying low-grade inflammation would improve the characterization of subsets of IBS patients in whom peripheral mechanisms may participate in specific symptom genesis and could be considered in the choice of the therapy.

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